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# Adding banding ligation is effective as rescue therapy to prevent variceal rebleeding in haemodynamic non-responders to pharmacological therapy

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ABSTRACT

*Background:* It is unknown which is the best therapy to treat haemodynamic non-responders to pharmacological therapy after variceal bleeding.
*Aim:* To evaluate the efficacy of adding banding ligation to drugs to prevent variceal rebleeding in haemodynamic non-responders to drugs.
*Methods:* Fifty-three cirrhotic patients with variceal bleeding underwent a hepatic venous pressure gradient (HVPG) measurement 5 days after the episode. Nadolol and nitrates were then titrated to maximum tolerated doses. A second HVPG was taken 14 days later. Responders (HVPG ≤12 mm Hg or ≥20% decrease from baseline) were maintained on drugs and non-responders had banding ligation added to drugs.
*Results:* Mean follow-up was 28 months. In 5 patients the second HVPG could not be performed because of early rebleeding. The remaining 48 patients were classified as responders ($n = 24$) and non-responders ($n = 24$), who had banding added. No baseline differences were observed between groups. Variceal rebleeding occurred in 12% of the 48 patients whose haemodynamic response was assessed. Responders on drug therapy presented a 16% rebleeding rate, whilst non-responders rescued with banding showed an 8% rebleeding rate. Rebleeding-related mortality was not different between groups.
*Conclusion:* In a HVPG-guided strategy, adding banding ligation to drugs is an effective rescue strategy to prevent rebleeding in haemodynamic non-responders to drug therapy.


## 1. Introduction

Recommended prophylaxis of variceal rebleeding includes the use of pharmacological therapy, non-selective β-blockers alone or with nitrates, combined with endoscopic band ligation [1–3]. In patients treated with drug therapy, the evaluation of the haemodynamic response by repeated measurements of the hepatic venous pressure gradient (HVPG) has been strongly recommended [1,2,4]. However, the clinical utility of this approach is unknown and the best therapies for non-responders to drugs are not determined. The available information regarding HVPG-guided therapy in variceal rebleeding is limited to few studies, with a low number of patients and using distinct strategies [5–8].

We have conducted the present uncontrolled trial to evaluate the efficacy of adding endoscopic banding ligation to drug therapy to prevent variceal rebleeding in patients treated with pharmacological therapy who were haemodynamic non-responders.

## 2. Patients and methods

### 2.1. Selection of patients

Between January 2006 and June 2010, 155 cirrhotic patients were admitted in the Bleeding Unit of our hospital because of acute oesophageal variceal bleeding. Bleeding was considered from oesophageal variceal origin when the emergency endoscopy performed within 12 h after admission showed any of the accepted criteria defining variceal bleeding [9]. Diagnosis of liver cirrhosis was based on usual clinical, biochemical and sonographic criteria. Acute bleeding was treated with somatostatin perfusion for 5 days and endoscopic therapy. Oral norfloxacin prophylaxis was given to all patients for 7 days. A total of 102 patients (Fig. 1) were

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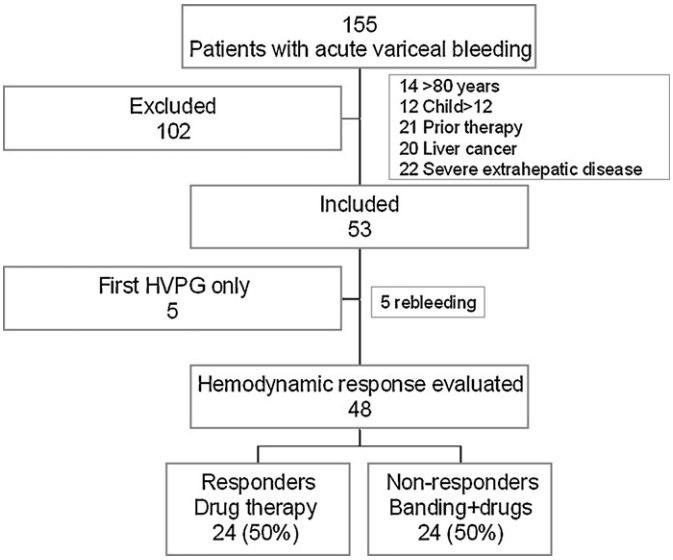


**Fig. 1.** Outcome of patients admitted for acute esophageal variceal bleeding. The most prevalent exclusion criteria are shown (HVPG, hepatic venous pressure gradient).

excluded from the trial because at least one of the following features was present: age older than 80 years ($n = 14$), Child-Pugh score >12 ($n = 12$), failure to control the index bleeding ($n = 8$), prior therapy with combined β-blockers plus nitrates or endoscopic variceal obliteration ($n = 21$), contraindications to β-blockers or nitrates ($n = 16$), advanced hepatocellular carcinoma ($n = 20$), severe associated conditions ($n = 22$), portal thrombosis ($n = 17$), and a HVPG <10 mm Hg ($n = 3$). The remaining 53 (34%) patients were included in the study after giving written informed consent. Time of inclusion was at the moment of the first haemodynamic study. The trial was approved by the ethics committee of our institution.

### 2.2. Study protocol

Five days after the index bleeding, a first hepatic haemodynamic study was performed after stopping somatostatin. Pharmacological therapy with β-blockers and nitrates was subsequently started. Once the maximum doses of both drugs were achieved, a second haemodynamic study was scheduled 5–7 days later. According to the haemodynamic response observed, patients were classified into 2 groups: responders when the HVPG was ≤12 mm Hg or had decreased <20% from baseline values [4] and non-responders when these haemodynamic targets were not achieved. Responder patients were maintained with the same pharmacological therapy and non-responders had banding ligation added to drug treatment.

Patients were followed at 3 months intervals at the outpatient Liver Clinic. History and examination assessed alcohol abstinence, compliance and adverse effects. Alcohol abstinence was assessed by direct anamnesis with the patient, separated interview with close relatives and unexpected determinations of alcoholemia. Compliance of drug therapy was also specifically inquired during the visit, and blood pressure and heart rate were measured in all patients at each follow-up visit. The study was continued for 3 months following the enrolment of the last patient. The primary end point was clinically significant rebleeding from portal hypertensive sources as defined by Baveno IV [10], which is equivalent to failure of secondary prophylaxis. Under these circumstances, an alternative therapy was instituted (e.g., banding in those on drug therapy, TIPS, or transplantation).

### 2.3. Treatments

#### 2.3.1. Drugs

Continuous pharmacological therapy was started immediately in all patients after the first haemodynamic study. Nadolol was given orally at an initial dose of 40 mg once daily. The dose was subsequently increased for a period of 5 days until intolerance appeared, the heart rate descended to 55 beats per minute or a 160 mg dose was reached. Oral isosorbide mononitrate was then started at 20 mg once at bedtime, followed by 20 mg BD for 1 day, and finally increased to 40 mg BD if tolerated.

#### 2.3.2. Banding

Patients assigned to banding underwent ligation within 24 h after the second haemodynamic study, in which they were classified as non-responders. Ligation was performed with commercial multiband devices at 3-week intervals until variceal obliteration had been achieved. Once eradicated patients underwent a follow-up endoscopy at 3 months, and at 6-month intervals thereafter. Additional sessions of ligation were conducted if varices reappeared.

### 2.4. Haemodynamic studies

Haemodynamic studies were performed after an overnight fast. Under local anaesthesia, a venous introducer was placed in the right femoral vein or internal jugular vein by the Seldinger technique. Under fluoroscopy, a 7F balloon-tipped catheter (Boston Scientific Medi-Tech, Natick, MA) was guided into the main right vein for measurements of wedged (occluded) and free hepatic venous pressures. The HVPG was obtained by subtracting the free from the wedged hepatic pressure gradient. All measurements were performed in triplicate, the average taken, and printed tracings of the haemodynamic studies were reviewed by investigators unaware of clinical data.

### 2.5. Statistics

Overall rebleeding and mortality analysis was conducted on an intention-to-treat basis. Follow-up was censored on the date when the patient was last seen, or the date of death or transplantation. Data are expressed as mean ± SD. Frequency data were compared using the $\chi^2$-test or the Fisher's exact test, when necessary. Quantitative variables were analysed with the Student's $t$-test. A $p$ value of <0.05 was required for statistical significance. Kaplan–Meier curves were constructed and compared with the log-rank test to evaluate the dynamics of rebleeding and survival. The SigmaStat 3.00 statistical package was used (SPSS Inc., Chicago, IL).

## 3. Results

### 3.1. Patient features and haemodynamic studies

Basal clinical and haemodynamic features of the 53 patients included in the study are shown in Table 1. Ten patients were already taking β-blockers before the index bleeding. Four patients with prior history of bleeding were included because they were following neither of the two pre-specified prophylactic strategies for variceal rebleeding (combined β-blockers plus nitrates or endoscopic variceal obliteration). The basal haemodynamic study was performed 5.1 ± 1 days after the index bleeding. The second HVPG measurement was not carried out in 5 patients (10%). These 5 patients presented variceal rebleeding 11.6 ± 5 days after the index bleeding and before the second haemodynamic study could be conducted; two of them died, and the other three had banding